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Do Non-Steroidal Anti-Inflammatory Drugs Increase the Risk for Non- or Mal-Union Following Acute Fracture? A Literature Review

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Introduction

Fracture healing has been shown to be dependent on the inflammatory cascade[1-4]. Prostaglandins appear to have a particularly important role[2]. Several studies have looked at cyclo-oxygenase-1 (COX-1) and cyclo-oxygense-2 (COX-2) knockout mice and identified impaired fracture healing specifically in the COX-2 knockout mice[1,2].

It has been hypothesized that based on this association between the COX-2 knockout animal models and impaired fracture healing, there could be a potentially negative impact on fracture healing with the concurrent use of non-steroidal anti-inflammatory drugs (NSAID) for analgesia use due to their impact on the COX-1 & COX-2 enzymes. Several animal models have produced results that show impaired fracture healing with the use of various NSAID medications[1,5].

NSAID medications are among the most commonly used analgesic medications world wide, and it was estimated in 2010 (updated 2015 data is expected to be published next year) that about 29 million adults in the United States regularly used NSAID medications at least three times per week for more than three months[6]. This was an increase of 41% from 2005 data[6].

Other analgesic options in fracture healing include acetaminophen, tramadol and opiates. Acetaminophen's main limitation is with hepatic disease. However, opiates are widely known throughout the medical community as well as the general public regarding the epidemic of abuse. In 2012, there were 259 million opiate prescriptions in the United States[7]. This is enough to provide each adult one bottle of medication[7].

In 2015, 20.5 million Americans over the age of 12 had a diagnosis of substance use disorder[7]. Of which, 2 million were related to prescription medications, including opiates, and almost 600,000 were related to heroin[7]. It is estimated that 4 out of 5 heroin users started by using prescription medications[7]. There were 20,000 lethal drug overdoses related prescription drugs and almost 13,000 related to heroin[7]. It is evident that medical providers have an integral role in reducing the number of opiate prescriptions through the use of alternative analgesic options.

The aim of this paper is to review the current literature on the potential risk between NSAID medication use in humans and the risk of non- or mal-union following acute fracture. It is important to have adequate evidence if we are to exclude the use of NSAID medications for their analgesic properties as that would likely increase the number of opiate prescriptions, which has obvious impacts on the current opiate epidemic. It is also an important topic as NSAID medications are a widely used over the counter analgesic option and therefore potentially an important educational topic between medical providers and their patients with fracture if there is found to be an increased risk for non- or mal-union.

Background

A retrospective case-control database review by Hernandez et al.[8] looked at 20 years worth of patient data (563 cases and 2,252 controls, n=2815)[8]. They found that the use of NSAID medications within 12 months prior to fracture increased the odds developing non- or mal-union as well as delayed union (adjusted OR 2.5, 95% CI: 2.0-3.2)[8] (Appendix Figure 1).

A retrospective cohort of 9.995 Medicare patients in the United States by Bhattacharyya et al.[9] looked at both NSAID medication and opiate exposure over 90 days post humeral shaft fracture. These findings showed that both NSAID medication and opiate exposure between days 0-30 and days 31-60 did not increase the risk of non-union[9]. It wasn't until days 61-90 that exposure to either medication increased the risk of nonunion (NSAID: RR 3.9, 95% CI 2.0-6.2; opiate: RR 2.7, 95% CI 1.5-5.2)[9] (Appendix Figure 2).

A randomized, double-blind, clinical trial by Drendel et al.[10] followed 244 pediatric patients with an arm fracture for up to 4 years and looked at ibuprofen and acetaminophen with codeine as analgesic options and the risk of nonunion or refracture at the same site. They identified 4 patients (1.6%) with refracture, of which 3 were treated with acetaminophen and 1 was treated with ibuprofen[10]. They did not identify any fracture nonunions in their study[10].

A retrospective study by Jeffcoach et al.[11] looked at NSAID medication use among long-bone fractures undergoing operative treatment (n=1,901; 42.1% femur, 23% tibia, and/or 22.5% humerus) and the risk for non- or mal-union. They identified 60

patients (3.2%) with non- or mal-union and found that those receiving an NSAID medication (mainly ibuprofen and ketorolac) during the inpatient postoperative setting were more likely to have a complication (OR 2.17; 95% CI 1.15-4.1; $p < 0.016$)[11] (Appendix Figure 3).

A retrospective study by Giannoudis et al.[12] compared 32 patients with diaphyseal fracture of the femur resulting in nonunion or appropriately healed fractures. They identified NSAID medication use (mainly ibuprofen and diclofenac), especially for longer than four weeks, as a predictor of increased odds of non-union (OR 10.74; 95% CI 3.55-33.23)[12] (Appendix Figure 4).

A randomized double-blind placebo controlled trial by Adolphson et al.[13] looked at 42 postmenopausal women with displaced Colles' fracture and whether the use of NSAID medication (peroxicam) for 8 weeks affected the rate of recovery. They used radiographic examinations to measure bone mineral content and found no significant difference between those treated with NSAID medication versus those treated with placebo[13].

A randomized double-blind trial by Davis et al.[14] in 1988 looked at 100 Colles' fractures treated with NSAID medication (flurbiprofen 50 mg TID) versus placebo. They found no difference in rates of non- or mal-union between the two groups[14].

A retrospective case-controlled study by Chuang et al.[15] followed patients from Taiwan who underwent hip fracture surgery over a 15 year time period and their risk for a second hip fracture. They concluded that the higher the mean daily dose ($p = 0.003$) as well as the longer time course ($p < 0.001$) of treatment with NSAID medications (ibuprofen, diclofenac, celecoxib) was associated with an increased risk of sustaining a

second hip fracture[15]. This study also found similar results when looking at paracetamol use and increased dose ($p = 0.026$ and $p = 0.009$ respectively)[15] (Appendix Figure 5).

Methods

The research topic presented here was conducted using a search of the PubMed database throughout the month of May 2017. The key search words utilized were: NSAID, non-steroidal anti-inflammatory drugs, fracture, non-union and mal-union. The goal of this particular study was to analyze human data regarding the use of NSAID medications following acute fracture and the potential risk of non- or mal-union. It was quickly noted that there is an overall lack of human clinical trials looking at this potential issue. Therefore, other review articles on the topic were reviewed as well for sources not identified through the above listed search methods to ensure adequate volume of material and data for comparison and analysis.

Discussion

Data looking at the effects of the inflammatory process on osteoblasts and osteoclasts indicate a positive impact that prostaglandins have on promoting osteogenesis[1-5]. However, human data is conflicting as noticed in the 8 human studies reviewed here – 3 studies found no statistically significant risk between NSAID medications and non- or mal-union[10,13,14], while 5 studies found statistically significant risks[8,9,11,12,15]. However, review, analysis and discussion of the data is necessary before a final conclusion can be made.

Most of these studies were conducted in a retrospective manner, which has many potential biases, namely the difficulty in predicting a cause and effect mechanism through this manner. The study conducted by Bhattacharyya et al.[9] had the largest number of subjects and they interestingly looked at specific time periods for NSAID medication use following acute fracture. With this interesting viewpoint, they identified that patients utilizing either NSAID medications or opiates for up to 3 months had a significant risk for non- or mal-union whereas either NSAID medications or opiates used for less than 2 months had no statistically significant risk. The authors of this study bring up an excellent question with this data in mind: could the data for the risk of NSAID medications and non- or mal-union reported in other studies simply be secondary to the pain associated with non- or mal-union necessitating increased use of analgesic options? This certainly seems plausible when considering that there is no known pharmacologic mechanism for opiates directly inhibiting osteogenesis.

With the results of Bhattacharyya et al.[9] in mind, it is also helpful to consider the 15-year study presented by Chuang et al.[15] In their retrospective look at various medication exposures on the occurrence of a second hip fracture (although this is not a non- or mal-union, this is still helpful to answer the question posed for this research topic as a second fracture can be considered a marker for osteogenesis), the authors stated that NSAID medications do present a significant risk for a second hip fracture in both their abstract and well as conclusion statements. However, upon careful review of the data, it should be noted that paracetamol was also associated with a significant risk for a second hip fracture. Interestingly, the authors did not mention this important finding in their discussion nor their conclusion. Similar to opiates, paracetamol does not have a known pharmacologic mechanism that would inhibit osteogenesis. This strengthens the argument by Bhattacharyya et al.[9] that the association identified between NSAID medications and non- or mal-union could be secondary to increased pain from non- or mal-union necessitating analgesic therapy. Also of note, the conclusion by Chuang et al.[15] stating that NSAID medications as a whole have an impact on the risk for a second hip fracture was only true for diclofenac, ibuprofen and celecoxib. Naproxen, etodolac and rofecoxib were not found to have a statistically significant impact. Therefore the authors came to a drastic conclusion that is not fully supported by their data.

The results from Giannoudis et al.[12] also retrospectively found a statistically significant risk between NSAID medication use and non-union when used for greater than four weeks. Considering the combination of this study along with those from Bhattacharyya et al.[9] and Chuang et al.[15], there seems to be a potential protopathic bias between NSAID medication exposure and non- or mal-union. In discussing analgesic

pharmacotherapy with multiple orthopedic providers, the general consensus is the need for analgesic pharmacotherapy for at most a few weeks. Therefore the prolonged analgesic pharmacotherapy courses seen in the studies by Bhattacharyya et al.[9] and Giannoudis et al.[12] are not typically experienced in general orthopedic practice.

Another interesting question to consider following these results from Bhattacharyya et al.[9] and Giannoudis et al.[12] would be the impact that proper fracture immobilization would have on long-term analgesic therapy needs. This would seem to be a likely association considering the role that proper fracture immobilization has on pain levels, however, a PubMed search including fracture, immobilization, pain and analgesic did not identify any specific studies looking at the potential association between proper immobilization and long-term analgesic therapy needs.

The results published by Hernandez et al.[8] are an interesting way to look at the potential risks that NSAID medications may have on non- or mal-union. Their study's design was able to identify risk factors for non- or mal-union before the fracture ever occurred. This does strengthen the mechanistic, in vivo and animal model studies that point towards a risk for NSAID medication use and non- or mal-union. This is a very important variable considering the previously mentioned data from 2010 on the frequency of regular NSAID medication use among the United States population.

The results from Jeffcoach et al.[11] found a risk between NSAID medication and fracture complications (non- or mal-union, and infection) when exposure to NSAID medication occurred acutely in the inpatient setting following fracture onset. This does add strength to the data from Hernadez et al.[8] regarding NSAID medication exposure before fracture ever occurred. It seems plausible mechanistically that perhaps

osteogenesis occurring in normal day-to-day life is negatively impacted by NSAID medications and therefore could decrease overall bone mineral density, which in turn could lead to fracture complications. However, a PubMed search including NSAID, non-steroidal anti-inflammatory drugs, osteoporosis and bone mineral density did not result in any studies reporting on this potential impact. Therefore, future studies are warranted to look into this potential mechanism. Another question that could be raised related to this search would be a potential association between chronic pain condition and reduced bone mineral density. Similarly, a PubMed search including chronic pain, bone mineral density and osteoporosis did not result in any studies reporting on this potential impact. This was discussed with an endocrinologist who was not aware of any data pertaining to this potential association.

Conclusion

Non- and mal-union following acute fracture has numerous impacts on quality of life and social issues (work productivity, family dynamics, etc.). Healthcare providers have an important role in assessing and managing various risks to decrease potential morbidity involved. The research question presented here, looking at NSAID medications as a possible risk factor for non- or mal-union, is an important topic for multiple reasons. First, NSAID medications are widely used both through prescriptions, and arguably more importantly over-the-counter. Secondly, if NSAID medications are to be avoided as an analgesic option following acute fracture, healthcare providers must utilize other analgesic options that have their own associated morbidity and mortality, namely the opiate epidemic.

NSAID medication use appears to have a mechanistic in-vivo and in-vitro animal risk for the development of non- and mal-union following fracture. However, human data is lacking to support total avoidance of this analgesic option for all patients. Based on the current literature review presented above, I recommend acetaminophen as first line analgesic therapy following acute fracture. Acetaminophen should be titrated as needed for pain control to the age-adjusted maximum recommended dose (ie. 4 grams per day for adults and 3 grams per day for geriatrics) before alternative analgesic options are introduced.

I recommend NSAID medications as second line analgesic therapy after reviewing pertinent patient comorbid conditions. Considering the mechanistic in-vivo and in-vitro animal data, it is recommended to avoid NSAID medication therapy in those

with reduced bone mineral density risk factors including, but not limited to, endocrine disorders such as osteoporosis, hyperparathyroidism, hypercortisolism and hyperthyroidism; rheumatologic disorders requiring high-dose or long-term glucocorticoid therapy such rheumatoid arthritis, gout, and lupus; oncologic disorders such as multiple myeloma and bone related cancers; and gastrointestinal esophageal reflux disease with high-dose or long-term proton-pump inhibitor therapy. Other obvious limitations to NSAID medication therapy aside from reduced bone mineral density include cardiovascular, gastrointestinal ulcer and renal conditions. If co-morbid conditions are identified, I recommend tramadol or other opiates as second-line analgesic therapy. However, if co-morbid conditions that could negatively impact bone mineral density are ruled out, NSAID medications should be utilized as second-line analgesic therapy and titrated as needed for pain control to their respective pain dosing regimens (ie. ibuprofen 2400 mg or naproxen 1250 mg per day) before consideration of tramadol or other opiates as a third-line analgesic therapy.

Obviously, attention should also be given towards appropriate immobilization of acute fractures to aid in minimizing the risk of developing non- or mal-union issues. In discussion with several orthopedic providers, it was identified that appropriate immobilization of acute fractures is a primary means of reducing pain. It would be reasonable to identify patients that are requiring prolonged analgesic therapy for longer than three weeks as having potentially improper immobilization of the fracture and therefore need appropriate interventions.

Obviously, there is a need for future, well-designed studies that look prospectively at NSAID medication exposure following acute fracture and the risk of non- or mal-union

issues. Other identified areas in need of research include potential associations between NSAID medications and chronic pain conditions as a risk factor for osteoporosis.

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Appendix

Figure 1

Characteristic	Nonunion Cases n = 401	Nonunion Controls n = 1,604	Nonunion Adjusted [a] OR (95% CI)	Malunion Cases n = 101	Malunion Controls n = 404	Malunion Adjusted [a] OR (95% CI)	Delayed union Cases n = 61	Delayed union Controls n = 244	Delayed union Adjusted [a] OR (95% CI)
Sex									
Male	191	728	1.0	48	173	1.0	29	121	1.0
Female	210	876	0.92 (0.72–1.2)	53	231	0.83 (0.51–1.4)	32	123	0.98 (0.51–1.9)
Age quartiles [b]									
18–29	81	355	1.0	22	85	1.0	8	48	1.0
30–49	122	439	1.0 (0.75–1.4)	30	108	0.89 (0.44–1.8)	31	76	1.8 (0.68–4.8)
50–64	110	365	0.99 (0.69–1.4)	25	98	0.71 (0.35–1.5)	16	56	1.2 (0.41–3.6)
65–79	88	445	0.69 (0.46–1.0)	24	113	0.64 (0.30–1.4)	6	64	0.38 (0.10–1.4)
BMI category [c]									
< 18.5	8	32	0.95 (0.42–2.2)	1	8	0.44 (0.05–3.9)	2	9	1.0 (0.18–6.1)
18.5–24	137	502	1.0	33	120	1.0	15	80	1.0
25–30	99	327	1.1 (0.81–1.5)	25	90	1.0 (0.56–2.0)	18	58	1.8 (0.74–4.1)
> 30	42	164	0.80 (0.54–1.2)	14	36	1.4 (0.61–3.2)	12	27	2.0 (0.76–5.4)
Unknown	115	579	0.72 (0.53–0.98)	28	150	0.57 (0.30–1.1)	14	70	1.1 (0.45–2.7)
Smoking status									
Never	158	680	1.0	50	178	1.0	30	95	1.0
Former	65	174	1.7 (1.2–2.4)	12	37	1.1 (0.52–2.4)	7	42	0.66 (0.25–1.7)
Current	108	391	1.1 (0.86–1.5)	27	97	0.89 (0.51–1.6)	18	68	0.84 (0.41–1.7)
Unknown	70	359	0.76 (0.53–1.1)	12	92	0.36 (0.17–0.78)	6	39	0.49 (0.17–1.4)
Drinking status [c]									
Never	51	182	1.0	11	54	1.0	8	20	1.0
Former	4	14	0.65 (0.20–2.1)	2	5	2.6 (0.44–16)	0	1	Too few cases
Current	223	850	0.89 (0.62–1.3)	69	205	1.7 (0.78–3.6)	45	161	0.87 (0.33–2.3)
Unknown	123	558	0.79 (0.52–1.2)	19	140	0.51 (0.21–1.3)	8	62	0.38 (0.11–1.4)
Comorbidities									
Any malignant cancer	23	100	1.0 (0.62–1.6)	6	19	1.4 (0.50–3.8)	1	17	0.29 (0.04–2.4)
Type-I diabetes	18	31	2.4 (1.3–4.3)	4	8	2.1 (0.58–7.2)	1	3	1.3 (0.12–15)
Type-II diabetes	17	32	2.2 (1.2–4.0)	4	11	1.5 (0.46–4.7)	4	5	5.8 (1.2–29)
Osteoporosis	15	60	1.1 (0.61–2.0)	1	11	0.41 (0.05–3.3)	2	16	0.72 (0.14–3.6)
Hypothyroidism	16	60	1.1 (0.64–2.0)	3	19	0.68 (0.18–2.6)	2	6	1.5 (0.26–8.7)
Rheumatoid arthritis [c]	18	31	2.1 (1.1–3.9)	1	9	0.35 (0.04–2.8)	0	3	Too few cases
Peripheral vascular disease	3	14	Too few cases	1	2	2.6 (0.22–31)	0	2	Too few cases
Medication use									
Any steroids [c]	44	143	1.3 (0.87–1.8)	8	33	0.79 (0.34–1.8)	6	26	0.85 (0.30–2.4)
Any NSAIDs [d]	164	350	2.5 (2.0–3.2)	38	87	2.7 (1.6–4.6)	25	46	2.9 (1.5–5.8)
Anticonvulsants	11	45	0.94 (0.48–1.8)	4	17	0.89 (0.28–2.8)	1	13	0.27 (0.03–2.1)
Hormone therapy	22	56	1.6 (0.92–2.7)	4	16	1.0 (0.32–3.4)	2	8	0.76 (0.14–4.0)
Thyroid hormone therapy	17	66	1.1 (0.63–1.9)	4	19	0.95 (0.29–3.1)	2	5	2.2 (0.35–14)
Bone-loss therapy	18	61	1.4 (0.79–2.5)	3	16	0.84 (0.22–3.1)	3	15	1.0 (0.23–4.6)
Anticoagulants [c]	4	28	0.82 (0.28–2.4)	2	7	1.2 (0.24–6.4)	2	4	2.8 (0.31–25)
Antibiotics [c]	157	605	0.96 (0.76–1.2)	46	147	1.4 (0.87–2.2)	21	82	0.77 (0.41–1.5)
Chemotherapy									
Falls	20	72	1.2 (0.72–2.1)	5	15	1.4 (0.46–4.1)	2	16	0.74 (0.15–3.6)
Motor vehicle accident	8	14	2.3 (0.96–5.7)	0	2	Too few cases	4	3	7.4 (1.4–39)

[a] All odds ratios were adjusted for age and sex.
[b] Also adjusted for smoking and NSAIDs.
[c] Also adjusted for NSAIDs.
[d] Also adjusted for steroids.

Figure 2

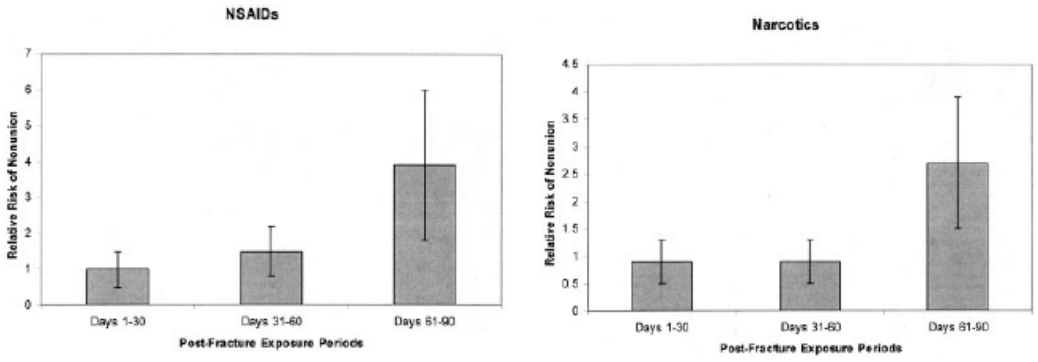

Figure 3

TABLE 5. Adjusted ORs for Complication Occurrence (Full Model)

Variable	Adjusted OR*	95% CI		*p*
		Lower	Upper	
NSAID use	2.17	1.15	4.10	0.016
Tobacco use	3.19	1.84	5.53	<0.001
Open fracture	3.11	1.60	6.03	0.001
Fall injury	0.37	0.17	0.79	0.011
MVC injury	0.51	0.27	0.96	0.037
ISS	1.01	0.99	1.04	0.380

*Adjusted OR, odds of complication occurrence adjusting for NSAID use, ISS, tobacco use, open fracture, fall injury, and MVC injury.

Figure 4

Table V. Predictors of primary interest for nonunion

Predictor	Odds ratio (95% CI)	p value
Reaming	1.83 (0.68 to 5.19)	0.275
Smoking	2.29 (0.85 to 6.08)	0.107
NSAIDs	10.74 (3.55 to 33.23)	0.000

Figure 5

Table 2 Medication use (paracetamol, dexamethasone, and NSAIDs) in Cases and Controls

Variables	Cases ($n = 94$)	Controls ($n = 461$)	*P* Value
Paracetamol, no. (%)	34 (35.8)	83 (18.1)	0.026*
MDD*, mg (SD)	605.6 (103.4)	496.0 (127.9)	0.009*
Aspirin, no. (%)	9 (9.9)	46 (10.0)	0.491
MDD, mg (SD)	105.6 (57.9)	101.2 (53.9)	0.569
Diclofenac, no. (%)	39 (41.7)	71 (15.4)	<0.001*
MDD, mg (SD)	206.9 (59.4)	116.1 (99.1)	<0.001*
Ibuprofen, no. (%)	26 (28.1)	93 (20.1)	<0.001*
MDD, mg (SD)	439.9 (115.9)	257.6 (85.0)	<0.001*
Naproxen, no. (%)	7 (7.4)	30 (6.5)	0.643
MDD, mg (SD)	485.2 (184.9)	451.0 (150.1)	0.583
Nabumetone, no. (%)	8 (9.0)	47 (10.1)	0.217
MDD, mg (SD)	1055.7 (479.3)	1014.7 (609.7)	0.506
Etodolac, no. (%)	13 (13.6)	54 (11.8)	0.416
MDD, mg (SD)	552.0 (50.1)	590.5 (33.9)	0.563
Celecoxib, no. (%)	22 (23.1)	44 (9.5)	<0.001*
MDD, mg (SD)	305.3 (98.8)	198.2 (100.1)	<0.001*
Rofecoxib, no. (%)	11 (11.6)	57 (12.3)	0.086
MDD, mg (SD)	70.6 (6.6)	75.7 (9.8)	0.057
Dexamethasone, no. (%)	37 (39.4)	76 (16.5)	<0.001*
MDD, mg (SD)	9.8 (7.5)	4.0 (3.9)	<0.001*

*MDD, mean daily dose
* *P* value <0.05 is significant and all analysis was done by logistic regression model in SAS 9.2

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